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Early Illness Features Associated with Mortality in the Juvenile Idiopathic Inflammatory Myopathies

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Abstract

Objectives—Because juvenile idiopathic inflammatory myopathies (JIIM) are potentially life-threatening systemic autoimmune diseases, we examined risk factors for JIIM mortality.

Methods—Mortality status was available for 405 patients (329 juvenile dermatomyositis [JDM], 30 juvenile polymyositis [JPM], 46 juvenile connective tissue disease–associated myositis [JCTM]) enrolled in nationwide protocols. Standardized mortality ratios (SMR) were calculated using United States population statistics. Cox regression was used to assess univariable associations with mortality, and random survival forest (RSF) classification and Cox regression for multivariable associations.

Results—Of 17 deaths (4.2% overall mortality), 8 (2.4%) were in JDM patients. Death was related to the pulmonary system, primarily interstitial lung disease (ILD), in 7 patients, gastrointestinal in 3, multisystem in 3, and of unknown etiology in 4 patients. The SMR for JIIM overall was 14.4 [95% confidence interval (CI) 12.2, 16.5] and 8.3 [95% CI 6.4, 10.3] for JDM. The top mortality risk factors in the univariable analysis included clinical subgroup (JCTM, JPM), anti-synthetase autoantibodies, older age at diagnosis, ILD and Raynaud's phenomenon at diagnosis. In multivariable analyses, clinical subgroup, illness severity at onset, age at diagnosis, weight loss and delay to diagnosis were the most important predictors from RSF; clinical subgroup and illness severity at onset were confirmed by multivariable Cox regression.

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Conclusions—Overall mortality was higher in JIIM patients, and several early illness features were identified as risk factors. Clinical subgroup, anti-synthetase autoantibodies, older age at diagnosis, and ILD are also recognized as mortality risk factors in adult myositis.

Keywords

juvenile idiopathic inflammatory myopathy; myositis; mortality; juvenile dermatomyositis; polymyositis; overlap myositis

The juvenile idiopathic inflammatory myopathies (JIIM) are rare, systemic autoimmune disorders characterized by proximal muscle weakness, skin rashes and the potential for involvement of other systems, including pulmonary, cardiac and gastrointestinal systems (1). Juvenile dermatomyositis (JDM), juvenile polymyositis (JPM) and juvenile connective tissue disease–associated myositis (JCTM) are the most common clinical phenotypes of JIIM (2). Distinct myositis autoantibody phenotypes are recognized in JIIM, and they are similar to those present in adult idiopathic inflammatory myopathies (IIM) (3). In general, although JIIM are serious illnesses that can result in death, it is uncommon. The factors associated with mortality in adults with IIM have been well studied (4–14). However, risk factors for mortality have not been examined in JIIM.

Prior to routine use of corticosteroids and other immunosuppressive therapies as the standard of care treatment for JIIM, more than one third of children with JDM died (15). The mortality rate has decreased markedly since those medications were introduced to treat JIIM, with recent reviews describing mortality rates of less than 2% (1, 16). However, specific data regarding mortality rates for JIIM have been infrequently obtained. A large pediatric rheumatology registry that included 662 children with JDM diagnosed between 1992 and 2001 in the United States identified 5 deaths (0.8%) and a standardized mortality ratio of 2.64 (17). In addition, two recent, large cohort studies report mortality rates for JDM between 0.7% and 3.1% (18, 19). Those reports documented that although mortality is no longer common in JDM, it remains an important concern. Furthermore, there are no data concerning mortality in other JIIM clinical or autoantibody phenotypes.

Little is known about the factors associated with mortality in JIIM. The goal of this study was to determine demographic, clinical and laboratory features associated with death in patients with JIIM and to compare them with risk factors for mortality previously identified in adult IIM patients.

Patients and Methods

Patients

Four-hundred forty-one patients with probable or definite JIIM (20) were enrolled in National Institutes of Health or Food and Drug Administration investigational review board–approved natural history protocols between March 1989 and April 2011; all patients or their parents provided informed consent. A physician questionnaire containing demographic, clinical and laboratory data; outcome information; and a blood sample were obtained as previously described (2). Approximately 85 illness features were assessed (see Supplementary Table 1). The referring physician recorded the month and year of each

illness feature, as well as the presenting signs and symptoms of illness; only those features present prior to or at the time of diagnosis were included. The questionnaire was completed at the time of enrollment by the referring physician. Illness severity at onset and onset speed were assigned by the enrolling physician using a categorical scale without knowledge of mortality outcome (2). For 70% of patients, a pediatric rheumatologist (LGR or GM) reviewed the medical record to confirm the questionnaire data and complete missing information. Sera were tested for myositis-specific autoantibodies and myositis-associated autoantibodies by using validated immunoprecipitation and immunoblotting methods (2).

Mortality status was established using the Social Security Death Index (SSDI). The SSDI was last searched April 11, 2011. Mortality status could not be confirmed in 22 patients due to insufficient identifying information; thus they were excluded. Fourteen non-American patients were also excluded. This left 405 patients (329 with JDM, 30 with JPM and 46 with JCTM) in this study. The cause of death was determined through death certificates and/or review of clinical charts.

Methods

Statistical analysis was conducted using Stata/IC 10.1 for Windows (StataCorp LP, College Station, TX). Continuous variables were summarized using median and interquartile range. Comparisons of proportions were made using Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test. This analysis was considered exploratory, so no corrections for multiple comparisons were made.

The sex-adjusted standardized mortality ratio (SMR) for this cohort was calculated using the life table for the US population for 1999–2001 (21). The yearly hazards were calculated using the method described by Therneau and Offord (22), and the cumulative hazard was determined as the sum of the yearly hazards. Expected deaths were then calculated and compared to observed deaths to generate the SMR. This was done for all JIIM and for each clinical subgroup (JDM, JPM, JCTM); SMRs for males and females in both groups were also calculated for all JIIM and JDM but not for JPM and JCTM due to small numbers of patients. Due to the small number of patients and short exposure time, the SMR calculation for JPM and JCTM was considered preliminary and confidence intervals were not calculated.

Univariable analysis was conducted using Cox regression analysis. Follow-up duration was defined as the time from diagnosis to date of death for patients who died and time from diagnosis to the last follow-up visit for those who were still alive. Ever hospitalized was included in the analysis, as it was assumed that most of the hospital admissions occurred at the time of diagnosis. Results for univariable analyses with $P \leq 0.10$ were reported, as this analysis was considered exploratory. Analyses were excluded when missing data resulted in 14 or fewer deaths being available. Consequently, fever, fatigue and dyspnea on exertion were excluded. To facilitate analysis, after the univariable analysis, disease subtype (JDM vs. not JDM) and onset severity (mild/moderate vs. severe/very severe) were dichotomized.

The multivariable analysis was conducted using a two-stage approach to further identify variables that were important predictors of mortality. First, we used random survival forests

(RSF) (23, 24) to identify and validate the predictors from a large group of candidate variables from the univariable Cox proportional hazards modeling. A conservative approach was taken by including all variables from the univariable Cox regression analysis with P<0.10 in order to avoid excluding potentially important variables. Second, we used multivariable stepwise Cox regression modeling to confirm the top RSF variables. Demographic, clinical, laboratory and outcome variables identified in the univariable analysis with $P \leq 0.10$ were entered in RSF models. The RSF analysis was performed using the R software package Random Survival Forests (version 2.13.1, 2011, The R Foundation for Statistical Computing) (23, 24). Each model was run 10 times using 20,000 trees per run. The average importance for each variable was calculated across runs, and then the average relative importance was obtained by assigning the variable with the highest importance a relative importance of 1.0. Error rates for the RSF models averaged 23.4%. Variables with the highest relative importance from the RSF analysis were then entered into a multivariable backwards-stepwise Cox regression model (a criterion of $P < 0.2$ was used to drop variables from model). A final multivariable Cox regression model was created with those variables with $P \leq 0.10$.

Results

Key demographic and illness features of the study population are shown in Table 1. Disease duration at study enrollment was a median of 1.6 years [25^{th}, 75^{th} percentile 0.5, 3.7 years] from diagnosis, median age at enrollment was 10.6 years [25^{th}, 75^{th} percentile 7.4, 15.3 years], and total follow-up since time of diagnosis was a median of 4.3 years [25^{th}, 75^{th} percentile 2.2, 7.5 years] for all patients. There were 17 deaths, for a 4.2% overall mortality rate. Of these, 8 deaths were in patients with JDM, yielding a JDM mortality rate of 2.4%. Two deaths were in patients with JPM, and 7 deaths were in patients with JCTM, for mortality rates of 6.7% and 15.2%, respectively. The median age at death was 18.4 years (25^{th}, 75^{th} percentile 16.6, 27.4 years) and disease duration at the time of death ranged from 0.1 to 38.5 years after diagnosis, with a median disease duration of 5.6 years at the time of death. Death occurred more frequently in patients who were older at diagnosis (median 14.7 years in those deceased vs. 7.4 years in those alive). Patients with severe illness at onset had a higher mortality rate than those with mild or moderate illness at onset. Patients with certain myositis autoantibodies, including any anti-aminoacyl tRNA synthetase autoantibodies, as well as anti-alanyl tRNA synthetase, anti-Ku or anti-La autoantibodies were more likely to have died than patients without these autoantibodies (Table 1).

The SMR for JIIM overall was 14.4 [95% confidence interval (CI) 12.2, 16.5]. The SMR for females with JIIM was 18.3 [95% CI 16.6, 20.1] and for males with JIIM was 7.1 [95% CI 5.9, 8.4. The overall SMR for JDM was 8.3 [95% CI 6.4, 10.3], while the SMR for females and males with JDM was 10.7 [95% CI 9.1, 12.3] and 3.3 [95% CI 2.2, 4.4], respectively. The overall SMR for JPM was 30.7 and the overall SMR for JCTM was 66.9. Females had a larger SMR for JIIM overall and for JDM, but no difference was seen in the univariable analysis for gender (P=0.6).

The primary causes of death were pulmonary in 7 patients, gastrointestinal in 3 patients and multisystem 3 patients. Pulmonary causes were a contributing factor in 2 of the multisystem

deaths (Table 2). Most of the pulmonary deaths resulted from complications of ILD. Gastrointestinal deaths were related to complications of gastrointestinal ulceration and/or vasculopathy. In 4 patients, the cause of death was not available.

In exploratory univariable analysis, 21 illness features were associated with a higher risk of mortality ($P < 0.10$) (Table 3). Clinical subgroup was strongly associated with a higher risk or mortality; the risk of mortality was highest for JCTM, moderate for JPM and lowest for JDM. One of the features most strongly associated with mortality was having an aminoacyl-tRNA synthetase autoantibody (particularly anti-alanyl-tRNA synthetase autoantibodies). All of these patients died of complications of ILD. Other autoantibodies associated with a higher risk of mortality included anti-Ku, anti-La, and anti-Sm autoantibodies, although these were each present in only one patient who died. Older age at illness onset and at diagnosis, dysphagia and abdominal perforation as the first presenting features of illness, as well as ILD, Raynaud's phenomenon and dysphonia preceding or at diagnosis were features more strongly associated with a higher risk of mortality. Gottron's papules were associated with a reduced risk of mortality ($HR < 1.0$). Some of these illness features were observed rarely (for example, dysphagia and abdominal perforation at illness onset, each present in only one patient who died).

Results of the RSF modeling are summarized in Table 4. Relatively few features had mean relative importance values greater than 0. The variables with the highest importance were clinical subgroup, severity at onset, older age at diagnosis, weight loss and delay to diagnosis. In the multivariable regression modeling (Table 5), the features that were independently associated with risk of death were clinical subgroup and illness severity at onset.

Discussion

This study identified several illness features that were associated with a higher risk of death in this large cohort of patients with JIIM. This is the first study to investigate mortality risk factors in JIIM and is an important step in understanding risk factors for death in these rare illnesses. In this study, 17 (4.2%) of 405 patients with JIIM died, with an overall SMR of 14.4 (95% CI 12.2, 16.5), suggesting greater risk of mortality in patients with JIIM compared to the healthy population. It is difficult to be certain how the SMR relates to the actual mortality rate in these illnesses. For example, although this study enrolled patients without consideration of disease severity, it is not known whether disease severity influenced the likelihood of study enrollment. For these reasons, our results might overestimate or underestimate the actual mortality rate for JIIM. Also, in calculating the SMR, we used life-table data for 1999–2001, which may provide only a crude estimate of the SMR, as our JIIM patients died between 1995 and 2007. Finally, with the small number of deaths, our estimates of the SMR are likely quite unstable. Females in our study had higher SMR for JIIM overall and for JDM, but no difference was seen between genders in the univariable analysis. There are some potential explanations for this discrepancy. Our cohort may have been too small to show this difference in the univariable analysis. However, it is more likely that the difference in SMR is related to differences in mortality

rates in the general population, as males consistently have higher mortality rates over the age range of relevance in this study.

It is difficult to directly compare our results to previous data, as few studies exist. The only study to provide standardized mortality rates in children with JDM utilized a large registry in the United States that enrolled patients with a variety of pediatric rheumatic diseases diagnosed between 1992 and 2001 (17). Patients in that study had a mean of 7.9 years follow-up; the JDM-specific follow-up duration was not provided. Using SSDI data, those authors identified 5 deaths in 662 JDM patients (0.8%) and calculated the SMR to be 2.64 [95% CI 0.86, 6.17]. The JDM-specific mortality rate in our study was 2.4% (8 of 329 JDM patients with a mean follow-up duration of 1.6 years) and the overall SMR for JDM was 8.3 [95% CI 6.4, 10.3]. It appears that the mortality rate in our study was higher over a shorter period of time. However, given differences in methodology and limited details in the study by Hashkes et al (17), it is difficult to further evaluate the difference in mortality rates between the two studies.

We can also compare our results to recent cohort-based studies. In an international cohort of patients from Europe and Latin America with a mean follow-up duration of 7.7 years, Guseinova et al (18) described 15 deaths among 490 JDM patients (3.1%). In contrast, in the United Kingdom, McCann et al (19) reported only 1 death in 151 (0.7%) children with JIIM (including 120 JDM patients) with a mean follow-up duration of 3.1 years. Differences in these results may be attributable to differences in JIIM populations (geographic, ethnic and JIIM phenotype distribution), as well as differences in care and follow-up duration.

Comparisons between SMRs in children and adults are of limited value, given the higher baseline mortality rates in adults. Nevertheless, Limaye et al (8) calculated SMRs of 1.75 (95% CI 1.41, 2.15) for Australian adults with IIM, 1.56 [95% CI 1.12, 2.10] for polymyositis (PM) and 2.4 [95% CI 1.1, 4.55] for dermatomyositis (DM). That study included patients with inclusion body myositis, which has been shown to have a relatively lower mortality rate (25). Airio et al (4) reported an SMR of 2.92 [95% CI 2.48, 3.44] for Finnish patients with PM and DM combined. Kuo et al (7) found an SMR of 7.68 [95% CI 6.41, 9.01] in Taiwanese patients with DM and 5.29 [95% CI 4.28, 6.48] in patients with PM. Although the SMR values for our study are higher than those reported in these adult studies, it is not possible to conclude that JIIM is more serious or has a higher mortality rate than adult IIM.

When we consider the causes of death in our cohort of JIIM patients, pulmonary disease was the most common association. Of the 13 patients with known cause of death, it was the primary cause for 7 patients and an associated cause in 2 patients. This is consistent with findings from adult IIM studies (6, 12, 13). Only 3 of these patients had an anti-aminoacyl-tRNA synthetase autoantibody, suggesting that in JIIM there are additional factors contributing to the development of pulmonary disease. In contrast, cardiac disease was a contributing factor to death in only 3 JIIM patients, although it is an important factor in adult studies (6, 11). The cardiac disease in our study is similar to that described in adult myositis studies, which includes rhythm disturbances, conduction abnormalities, pericardial effusion, left ventricular dysfunction, myocarditis, cardiomyopathy and congestive failure (6, 11).

Finally, gastrointestinal bleeding or perforation was the cause of death in 3 patients. Although this cause of death is not described in adult studies, it is consistent with clinical experience in JIIM (16).

We identified, by univariable analysis, several illness features associated with a higher risk of death in JIIM patients. To avoid the problem of differential follow-up, we examined only those illness features present prior to or at the time of diagnosis. Factors that were associated with an increased risk of mortality included clinical subgroup, anti-aminoacyl-tRNA synthetase autoantibodies, older age at illness onset and at diagnosis, and some early illness features present prior to or at diagnosis, including ILD, Raynaud's phenomenon and dysphonia. Given the few deaths and many analyses conducted, these illness features should be confirmed in other JIIM cohorts.

The relative rarity and infrequent mortality of patients with JIIM are a major challenge in this kind of research. However, we used a variety of methods to determine significant illness features by univariable analyses and then conducted exploratory multivariable analyses. We used RSF, a novel statistical method which extends the machine-learning tool random forest to survival analysis, to examine the relationship of a number univariable factors and identify their relative importance in predicting the risk of mortality (Table 4) (23, 24). Random forests and RSF have been similarly used successfully by other investigators to determine mortality risk factors for other rheumatic illnesses, cardiovascular disease and malignancies (23, 26–28). Some of the risk factors that we identified, including clinical subgroup and ILD, are similar to those found in studies of adult IIM (6, 12–14).

The multivariable regression model confirmed and quantitated the strength of association of key illness features that were most associated with risk of mortality in JIIM, including clinical subgroup and illness severity at onset. These findings suggest that early disease severity is an important risk factor for death.

We compared risk factors for mortality in our study to those documented for adult IIM and found similarities and differences. Of the mortality features from our univariable analyses, those also described in adult IIM studies included older age at illness onset (4–6, 10–13, 29), delay in diagnosis or treatment (4, 5, 10), ILD (6, 12–14), anti-synthetase autoantibodies (8, 9, 30) and dysphagia (6). Our study in JIIM did not identify other important mortality risk factors that have been seen in adult IIM, such as malignancy (4, 5, 10–13), cardiac involvement and ischemic cardiovascular disease (6, 8, 11), skin ulcers (10, 13) and male gender (6, 11, 29). The presence of anti-SRP autoantibodies has been found to be a risk factor for death by some investigators (30), but not by others (31); anti-SRP autoantibodies did not appear to increase the risk of death in JIIM in our study. The rarity of cardiac disease in children, with lack of adequate follow-up into the adult years, and the rarity of malignancy in JIIM (2) may explain their absence as mortality risk factors for JIIM.

Our study also identified risk factors that have not been described in studies of adult IIM. For example, in the multivariable analysis, illness severity at onset was associated with a higher risk of death. Given the number of risk factors for death that are common between

children and adults with IIM, this novel risk factor warrants further study in adult IIM and confirmation in other JIIM populations.

Despite the careful conduct of this study, there are some important limitations. First, we had relatively few deaths to analyze, as death in JIIM has become uncommon. This limited our ability to conduct robust, multivariable modeling. Our results must therefore be considered preliminary and will require confirmation in additional large cohorts. Our univariable analysis results are simply presented using a very conservative cutoff of $P<0.1$, but limited conclusions are drawn. Inclusion of variables in the multivariable analysis (both RSF and Cox regression) is also based on a very conservative P-value cutoff, and it would not be appropriate to lower this as potentially important variables could be discarded prematurely. Also, because RSF is a predictive model rather than an associative model, it is possible that by filtering the features for RSF based on the results of univariable analyses, we have missed predictive features in the RSF. In contrast, the multiple testing used in the multivariable stepwise logistic regression modeling increases the risk of Type I statistical error and the possibility of false-positive results. However, given that the study was exploratory, we did not correct for multiple comparisons.

Although children were enrolled from many sites in North America, it is not known how well this cohort represents the entire population of JIIM. There are also limitations to the use of the SSDI. Although the SSDI allows most deaths to be identified, it is possible that some deaths or some study participants could have been missed. Finally, our study is limited by the fact that participants were enrolled over a period of 22 years. This allowed a large cohort to be assembled and facilitated the identification of 17 deaths, but the treatment of children with JIIM has changed considerably during that time. Our study did not examine the impact of therapy on mortality. A study by Schiopu et. al. examined the role of therapy as a risk factor for mortality in adults with IIM and found that patients receiving intravenous corticosteroids had a higher mortality rate, which was attributed to greater disease severity (29). While changes in treatment have certainly reduced mortality in JIIM, it is less clear if changes in treatment have affected predictors of mortality. Thus, the lack of treatment data in our study does not negate the relevance of our findings.

In conclusion, we conducted the first study of risk factors for mortality in patients with JIIM. Through the use of RSF as a novel statistical approach, we identified a number of illness features associated with an increased risk of death. Several of these have previously been identified as risk factors for mortality in adults with IIM and thus are likely to be true risk factors for mortality in JIIM as well, whereas others are novel. These new factors warrant additional study to confirm their association with mortality and contribution to JIIM outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1

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Significance and Innovations

- Mortality is increased in the juvenile idiopathic inflammatory myopathies.
- Risk factors for mortality in juvenile myositis have been identified and many of these are shared with adult IIM, including clinical subgroup, anti-aminoacyl-tRNA synthetase autoantibodies, older age at diagnosis, and interstitial lung disease.

Table 1

Baseline demographic features and myositis autoantibodies of 405 juvenile idiopathic inflammatory myopathy patients

	Alive at Last Follow-up (n=388)*	Deceased (n=17)*	P
Clinical subgroup			
JDM	321 (83%)	8 (47%)	
JPM	28 (7%)	2 (12%)	0.001†
JCTM	39 (10%)	7 (41%)	
Gender			
Female	281 (72%)	14 (82%)	0.6†
Male	107 (28%)	3 (18%)	
Race			
White	265 (68%)	13 (76%)	
Black	58 (15%)	3 (18%)	
Hispanic	24 (6%)	0	0.9†
Asian	7 (2%)	0	
Other	34 (9%)	1 (6%)	
Median age at diagnosis, years [25%, 75%]	7.4 [5.1, 11.6]	14.7 [9.0, 16.4]	0.001‡
Median diagnosis delay, months [25%, 75%]	4.0 [2.0, 9.0]	6.0 [2.0, 12.7]	0.5 ‡
Median age at study enrollment, years [25%, 75%]	10.5 [7.3, 15.1]	16.0 [10.5, 27.6]	0.005 ‡
Median disease duration at study enrollment, years [25%, 75%]	1.6 [0.5, 3.6]	0.6 [0.2, 10.5]	0.4‡
Median Disease Duration at Last Follow-up/Death, years [25%, 75%]	4.3 [2.2, 7.4]	5.6 [1.6, 9.8]	0.6‡
Onset speed			
Very slow (> 6 months)	136 (35%)	7 (47%)	
Slow (3–6 months)	112 (29%)	4 (27%)	
Moderate (< 3 months)	98 (25%)	2 (13%)	0.6†
Rapid (< 1 month)	36 (9%)	2 (13%)	
Very rapid (< 1 week)	3 (1%)	0	
Illness severity at onset			
Mild	40 (10%)	0	
Moderate	231 (60%)	7 (41%)	0.06†
Severe	105 (27%)	10 (59%)	
Very severe	9 (2%)	0	
Myositis autoantibodies			
Any aminoacyl-tRNA synthetase Abs	14 (4%)	3 (18%)	0.03†
Anti-histidyl-tRNA synthetase Abs (Jo-1)	9 (2%)	1 (6%)	0.4†
Anti-alanyl-tRNA synthetase Abs (anti-PL-12)	3 (0.8%)	2 (12%)	0.02†
Anti-Mi2 Abs	10 (3%)	0 (0%)	1.0†
Anti-p155/140 Abs	124 (33%)	3 (19%)	0.3†

	Alive at Last Follow-up (n=388)*	Deceased (n=17)*	P
Anti-MJ Abs	81 (21%)	1 (6%)	0.2†
Anti-SRP Abs	6 (2%)	0 (0%)	1.0†
Anti-PM-Scl Abs	11 (3%)	1 (6%)	0.4†
Anti-Ku Abs	1 (0.3%)	1 (6%)	0.01†
Anti-Ro Abs	26 (7%)	2 (12%)	0.3†
Anti-La Abs	2 (0.5%)	1 (6%)	0.1†
Anti-Sm Abs	5 (1%)	1 (6%)	0.2†

Abbreviations. JDM = juvenile dermatomyositis; JPM = juvenile polymyositis; JCTM = juvenile myositis associated with an underlying connective tissue disease; Abs = autoantibodies; SRP = signal recognition particle

*Totals may not add up due to data missing for some variables for some patients.

†Fisher's exact test.

‡Mann-Whitney U test.

Table 2

Causes of death in 17 patients with juvenile idiopathic inflammatory myopathies*

System	Diagnosis	Myositis Autoanti-bodies	Gender/Race	Age at Diagnosis (years)	Disease Duration at Death (years)	Cause of Death
Pulmonary	JCTM†‖	none	Female/White	15	0.3	Interstitial lung disease, progressive respiratory failure, acute cardiac failure‡
	JDM	PL-12	Female/White	15	1.4	Respiratory failure, pulmonary fibrosis§
	JDM	PL-12	Female/White	10	5.6	Interstitial lung disease, chronic interstitial pneumonitis‡§
	JCTM‖	Ku	Female/White	8	6.6	Interstitial lung disease (diffuse alveolar damage with marked interstitial fibrosis)‡§
	JDM	p155/140	Female/White	12	7.5	Interstitial lung disease, secondary pulmonary hypertension‡
	JCTM¶	Jo-1, Ro, La	Female/Black	17	9.5	Interstitial lung disease‡
	JCTM‖	none	Female/Other	5	12.6	Pulmonary hypertension; multiple spontaneous pneumothoraces; secondary scleroderma, severe malnutrition, superior mesenteric artery syndrome‡
Gastrointestinal	JPM	Ro	Male/White	1	0.5	Intestinal perforation‡
	JCTM†‖	Sm	Male/Black	15	4.0	Colon perforation resulting in *E. coli* sepsis‡
	JDM	p155/140	Female/White	7	10.3	Gastrointestinal hemorrhage‡
Multisystem	JPM	none	Female/White	16	0.1	Myocarditis, tachyarrhythmias, respiratory failure, pneumonia‡
	JDM	none	Female/Black	16	2.0	Acute respiratory distress syndrome; sepsis; congestive heart failure; intracranial hemorrhage‡
	JCTM#	none	Female/White	16	3.5	Liver failure, renal failure§
Unknown	JCTM‖	PM-Scl	Female/White	16	16.7	Unknown
	JDM	MJ	Female/White	14	31.7	Unknown
	JDM	none	Male/White	10	35.1	Unknown
	JDM	p155/140	Female/White	7	38.5	Unknown

Abbreviations. JDM = juvenile dermatomyositis; JPM = juvenile polymyositis; JCTM = juvenile myositis associated with an underlying connective tissue disease; PL-12=Anti-alanyl-tRNA synthetase autoantibodies; Ku=Anti-Ku autoantibodies; p155/140=Anti-p155/140 autoantibodies; Jo-1=Anti-histidyl tRNA synthetase autoantibodies; Ro=Anti-Ro autoantibodies; La=Anti-La autoantibodies; Sm=Anti-Sm autoantibodies; PM-Scl=Anti-PM-Scl autoantibodies; MJ=Anti-MJ autoantibodies.

*Patients were diagnosed between 1981 and 2002 and were a median of 18.4 years (25^{th}, 75^{th} percentile 16.6, 27.4 years) at the time of death

†Overlap of JDM and systemic lupus erythematosus.

[‡] Information from physician or medical record.

[§] Information from death certificate.

[||] Overlap of JDM and systemic sclerosis.

[¶] Overlap of JPM and Sjögren syndrome.

[#] Overlap of JPM and systemic lupus erythematosus.

Table 3

Summary of univariable Cox regression analyses relating risk of death and illness features

Illness Feature*	No. of Deaths (%)		Hazard Ratio [95% confidence interval]	P
	Illness Feature Absent	Illness Feature Present		
Clinical subgroup JDM vs. JCTM	JDM 8/329 (2.4%)	JCTM 7/46 (15.2%)	9.8 [3.1, 31.4]	<0.001
Clinical subgroup JDM vs. JPM		JPM 2/30 (6.7%)	7.0 [1.3, 37.7]	0.03
Illness severity at onset (mild/moderate vs. severe/very severe)	7/278 (2.5%)	10/127 (7.9%)	2.9 [1.1, 7.6]	0.03
Age at diagnosis (years)†	7.4 [5.1, 11.6]	14.7 [9.0, 16.4]	1.2 [1.1, 1.3]	<0.001
Age at onset (years)†	6.9 [4.5, 11.0]	12.3 [8.5, 15.0]	1.2 [1.1, 1.3]	0.002
Delay to diagnosis (months)†	4.0 [2.0, 9.0]	6.0 [2.0, 12.7]	1.02 [1.0, 1.0]	0.03
Clinical Features Present Prior to or at Diagnosis				
Dysphagia‡	14/389 (3.6%)	1/1 (100%)	375.5 [23.5, 6003.2]	<0.001
Abdominal perforati on‡	16/403 (4.0%)	1/1 (100%)	39.4 [4.8, 325.2]	0.001
Ever hospitalized	1/183 (0.6%)	15/208 (7.2%)	10.5 [1.4, 80.1]	0.02
Interstitial lung disease	12/385 (3.1%)	3/16 (18.8%)	9.8 [2.6, 37.1]	0.001
Raynaud's phenomenon	9/366 (2.5%)	7/31 (22.6%)	8.8 [3.2, 24.5]	<0.001
Gastroesophageal regurgitation	12/363 (3.3%)	3/31 (9.7%)	4.3 [1.2, 15.9]	0.03
Dysphonia	9/324 (2.8%)	6/64 (9.4%)	4.1 [1.4, 11.9]	0.009
"Shawl sign" rash	10/351 (2.9%)	5/36 (13.9%)	3.8 [1.3, 11.5]	0.02
Weight loss	7/270 (2.6%)	8/118 (6.8%)	2.9 [1.03, 8.0]	0.04
Abdominal pain	11/313 (3.5%)	5/75 (6.7%)	2.9 [0.9, 8.9]	0.07
Gottron's papules	7/85 (8.2%)	8/306 (2.6%)	0.3 [0.09, 0.8]	0.01
Myositis Autoantibodies				
Anti-Alanyl-tRNA synthetase Abs (anti-PL-12)	15/394 (3.8%)	2/5 (40%)	23.6 [4.7, 117.3]	<0.001
Anti-Ku Abs	16/397 (4.0%)	1/2 (50%)	18.3 [2.2, 147.9]	0.006
Any aminoacyl tRNA synthetase Abs	14/382 (3.7%)	3/17 (17.7%)	13.1 [3.4, 50.4]	<0.001
Anti-La Abs	16/396 (4.0%)	1/3 (33.3%)	12.2 [1.5, 96.5]	0.02
Anti-Sm Abs	16/393 (4.1%)	1/6 (16.7%)	7.2 [0.9, 56.2]	0.06

Abbreviations. JDM = juvenile dermatomyositis; JPM = juvenile polymyositis; JCTM = juvenile myositis associated with an underlying connective tissue disease; Abs=autoantibodies; PL-12=Anti-alanyl-tRNA synthetase autoantibodies.

*All illness features with P < 0.10 included.

†Median [25th, 75th quartiles] reported for those who did not die in the "Illness Feature Absent" column and for those who did die in the "Illness Feature Present" column.

‡First myositis symptom reported.

Table 4

Summary of random survival forest analysis relating risk of death and clinical features*

Illness Feature	Mean Relative Importance
Clinical subgroup (JDM vs. JPM/JCTM)	1.00
Illness severity at onset	0.33
Age at diagnosis	0.32
Weight loss	0.30
Delay to diagnosis	0.23
“Shawl sign” rash	0.08
Abdominal pain	0.07
Age at onset	0.06
Gottron’s papules	0.05
Anti-Ku Abs	0.00
Anti-Sm Abs	0.00
Anti-La Abs	0.00
Any aminoacyl tRNA synthetase Abs	0.00
Anti-alanyl-tRNA synthetase (anti-PL-12) Abs	0.00
Dysphagia	0.00
Interstitial lung disease	0.00
Abdominal perforation (first symptom)	0.00
Ever hospitalized	0.00
Gastroesophageal regurgitation	− 0.04
Raynaud’s phenomenon	−0.04
Dysphonia	− 0.19

Abbreviations. JDM = juvenile dermatomyositis; JPM = juvenile polymyositis; JCTM = juvenile myositis associated with an underlying connective tissue disease; Abs=autoantibodies.

* Mean importance values for 10 runs are compared to the highest mean importance value. All features with P<0.10 in Cox regression are included.

Table 5

Summary of final multivariable Cox regression analyses relating risk of death and illness features

	Variable	Hazard Ratio [95% confidence interval]	P
Initial Cox regression model with backwards-stepwise selection*	Clinical subgroup (JDM vs. JPM/JCTM)	4.8 [1.2, 19.6]	0.03
	Illness severity at onset	5.1 [1.4, 17.9]	0.01
	Age at diagnosis	1.1 [0.98, 1.3]	0.09
Final Cox regression model	Clinical subgroup (JDM vs. JPM/JCTM)	8.6 [2.5, 30.2]	0.001
	Illness severity at onset	5.7 [1.6, 19.5]	0.006

Abbreviations. JDM = juvenile dermatomyositis; JPM = juvenile polymyositis; JCTM = juvenile myositis associated with an underlying connective tissue disease.

* Multivariable Cox regression model began with clinical subgroup (JDM vs. JPM/JCTM), illness severity at onset, age at diagnosis, weight loss and delay to diagnosis before backwards-stepwise selection; 308 patients were included in the model.